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Neonatal thyroid function: prematurity, prenatal steroids, and respiratory distress syndrome

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SUMMARY Indices of thyroid function were measured in 97 preterm infants at birth and at 5, 10, and 15 days of age. Triiodothyronine uptake, free thyroxine index, thyroxine, free thyroxine, triiodothyronine, reverse triiodothyronine, and thyroxine binding globulin values at birth correlated with gestational age, whereas thyroid stimulating hormone values did not. Treatment with steroids prenatally had no apparent effect on thyroid function at birth or postnatally. Infants developing respiratory distress syndrome had normal values for all indices at birth. These infants had significantly lower thyroxine, free thyroxine index, free thyroxine, and triiodothyronine values at 5 days of age, while thyroid stimulating hormone values remained normal. This alteration in thyroid function was interpreted as being secondary to respiratory distress syndrome. Gestational maturity and respiratory distress syndrome, if present, must be taken into account when evaluating thyroxine variables in preterm infants, whereas measurement of thyroid stimulating hormone as the screen for congenital hypothyroidism circumvents these considerations.

Thyroid hormone concentrations in the preterm infant at birth correlate with gestational age,[1 2] so evaluation of thyroid function in preterm infants should take account of scale of prematurity. Such a consideration has shown that postnatal thyroxine, free thyroxine index, and triiodothyronine values also correlate with gestational age.[2 3] Previous studies of thyroid function in preterm infants suffering respiratory distress syndrome have aggregated the subjects and reported low[4–7] or normal[8–10] mean values for thyroid hormones at birth. Postnatal mean values have shown a transient to protracted depression of one or more variables.[4 6 8 9 11 12] Whether this postnatal depression of thyroid function represents a continuation of the low values observed at birth or is a consequence of respiratory distress syndrome has been debated.[8 9 12] This study aimed to assess thyroid function longitudinally in preterm infants suffering respiratory distress syndrome, while simultaneously taking account of scale of prematurity. The possible effect that prenatal administration of steroids might have on thyroid hormone concentrations in the preterm infant was also examined.

Subjects and methods

Ninety seven preterm neonates born between 29 and 37 weeks' gestation were studied. Informed maternal consent and approval of the research ethical committee of Wellington Clinical School had been obtained. Gestational maturity was estimated from maternal menstrual history and confirmed by physical examination.[13] Sixty two infants maintained good health, 19 of whom, born at gestational ages between 29 and 33 weeks, had been treated prenatally with a glucocorticoid (dexamethasone or betamethasone) for at least 24 hours before delivery. Thirty five infants developed respiratory distress syndrome as defined by clinical and radiological criteria,[14] all of whom survived.

Seventy eight cord serum samples were recovered, and capillary serum samples were collected at 5, 10, and 15 days of age. These were held at −20°C until assay. Triiodothyronine uptake and thyroxine, free thyroxine, triiodothyronine, reverse triiodothyronine, thyroxine binding globulin, and thyroid stimulating hormone concentrations were measured by radioimmunoassay. The methods, modifications, and variabilities of the assays used have been described in detail.[15 16] The free thyroxine index was calculated as the product of thyroxine and triiodothyronine uptake. All samples from individual subjects were run randomised within the same assay.

The data were stored and processed by computer

after logarithmic transformation of individual hormone values. Statistical analyses included multiple linear regressions, partial correlation coefficients, and analysis of covariance.

Results

The ranges for thyroid function indices observed at birth and at 5, 10, and 15 days of age in the three groups of subjects are presented in Table 1. A preliminary analysis comparing regression equations showed that the linear relations between cord hormone values and gestational age and birth weight for the three groups were not significantly different ($p > 0.05$). Therefore, all the cord sera data were included in estimating the correlations of the cord hormone values with gestational age and birth weight (Table 2). As gestational age and birth weight were significantly correlated ($r=0.73$, $p<0.0001$), however, the partial correlation coefficients of the cord hormone values with gestational age controlled for birth weight and with birth weight controlled for gestational age were also estimated (Table 2). The partial correlations of the cord hormone values with birth weight controlled for gestational age were not significant, so only gestational age was included as a covariate in the analysis of covariance to compare the hormone values of the three groups at birth and at 5, 10, and 15 days of age. This analysis showed significant differences between the groups on day 5 for free thyroxine index and thyroxine, free thyroxine, and triiodothyronine concentrations (Table 1).

Table 1 *Serum concentrations of thyroid hormones, thyroxine binding globulin, and thyroid stimulating hormone and values for triiodothyronine uptake and free thyroxine index in healthy preterm neonates (group 1), healthy preterm neonates treated prenatally with glucocorticoids (group 2), and preterm neonates suffering respiratory distress syndrome (group 3) at birth, 5, 10, and 15 days of age. Results are ranges*

	Group 1 (n=43)	*Group 2 (n=19)*	*Group 3 (n=35)*	*Significance of difference between groups (analysis of covariance)*
Thyroxine (nmol/l):				
Cord	60–178	66–176	54–178	
Day 5	102–310	78–182	44–270	p<0·0001 (Group 1>Group 3, p<0·0001; Group 2>Group 3, p<0·01)
Day 10	112–210	76–160	50–236	
Day 15	104–202	82–160	90–262	
Triiodothyronine uptake:				
Cord	0·75–1·11	0·71–1·23	0·80–1·20	
Day 5	0·68–1·01	0·68–1·17	0·68–1·22	
Day 10	0·60–1·13	0·70–1·14	0·69–1·12	
Day 15	0·75–1·00	0·78–1·17	0·71–1·18	
Free thyroxine index:				
Cord	61–174	73–145	66–150	
Day 5	99–252	66–129	42–219	p<0·001 (Group 1>Group 3, p<0·001; Group 2>Group 3, p<0·02)
Day 10	104–196	75–138	55–234	
Day 15	96–180	75–138	84–220	
Free thyroxine (pmol/l):				
Cord	6·4–20·6	9·0–16·7	7·7–20·6	
Day 5	7·7–29·9	6·4–20·6	5·1–24·5	p<0·01 (Group 1>Group 3, p<0·01; Group 2>Group 3, p<0·02)
Day 10	7·7–24·5	6·4–19·3	6·4–25·7	
Day 15	6·4–25·7	5·1–21·9	9·0–27·0	
Triiodothyronine (nmol/l):				
Cord	0·3–1·3	0·3–1·1	0·3–1·1	
Day 5	1·0–3·4	0·8–1·9	0·6–2·1	p<0·02 (Group 1>Group 3, p<0·01)
Day 10	1·6–4·3	1·2–2·5	1·0–2·8	
Day 15	1·5–3·5	1·3–2·7	1·2–3·1	
Reverse triiodothyronine (nmol/l):				
Cord	2·3–8·6	4·0–9·5	2·3–8·6	
Day 5	1·3–4·4	1·4–3·6	1·6–3·9	
Day 10	1·3–2·5	0·9–2·4	0·8–3·3	
Day 15	0·9–2·3	0·7–1·6	0·8–2·4	
Thyroxine binding globulin (mg/l):				
Cord	14·8–41·0	19·8–34·5	17·0–41·3	
Day 5	21·3–36·2	18·8–36·0	17·0–34·0	
Day 10	20·8–34·8	19·3–33·5	18·5–39·5	
Day 15	21·8–31·3	18·5–32·8	19·3–36·0	
Thyroid stimulating hormone (mU/l):				
Cord	3·3–16·0	3·7–11·8	3·0–16·3	
Day 5	0·8–11·6	0·8–11·0	0·8–8·9	
Day 10	1·3–7·0	1·0–6·7	0·8–7·2	
Day 15	1·1–9·9	1·3–5·5	1·1–10·2	

Conversion: SI to traditional units—Thyroxine: 1 nmol/l≈0·08 μg/100 ml. Triiodothyronine: 1 nmol/l≈65·1 ng/100 ml.

Table 2 *Correlation coefficients (r) and partial correlation coefficients between indices of thyroid function at birth, gestational age, and birth weight for preterm neonates*

	r With gestational age	*r With birth weight*	*Partial correlation coefficient with*	
			Gestation age controlled for birth weight	*Birth weight controlled for gestational age*
Thyroxine	0·42‡	0·32†	0·29†	−0·07
Triiodothyronine uptake	−0·46§	−0·31†	−0·39‡	0·16
Free thyroxine index	0·24*	0·21	0·12	0·02
Free thyroxine	0·31†	0·26*	0·16	0·01
Triiodothyronine	0·54§	0·50§	0·26*	0·11
Reverse triiodothyronine	−0·52§	−0·46§	−0·29†	−0·05
Thyroxine binding globulin	0·42‡	0·39‡	0·18	0·08
Thyroid stimulating hormone	0·06	0·02	0·14	−0·12

*p<0·05.
†p<0·01.
‡p<0·001.
§p<0·0001.

Discussion

These studies, in the first instance, confirmed that thyroid hormone concentrations in the preterm infant at birth correlate with gestational age.[1 2] Hence the need to control for gestational maturity when assessing whether prenatal treatment with steroids or respiratory distress syndrome might influence indices of thyroid function. Prenatal treatment of preterm infants with glucocorticoids had no apparent effect on thyroid function at birth or subsequently, in that the results of the group treated were not significantly different, at any sampling interval, from those of the healthy untreated group. The thyroid hormone concentrations at birth and at 10 and 15 days of age in preterm infants suffering respiratory distress syndrome were comparable with those observed in healthy preterm infants, whereas the day 5 thyroxine, free thyroxine, and triiodothyronine concentrations and free thyroxine index values were significantly lower. Thyroid stimulating hormone concentrations were normal at each sampling interval. These observations support the view that the postnatal depression of thyroid function is secondary to respiratory distress syndrome,[8 9] with the transient changes being comparable with the altered thyroid function seen in term neonates suffering non-thyroidal illnesses.[17]

The thyroxine and thyroid stimulating hormone data are relevant to the assessment of thyroid state, particularly routine screening, in the preterm neonate. Gestational maturity must be taken into account when interpreting thyroxine screening results.[2 18] This situation is not complicated by giving glucocorticoids prenatally to promote lung maturation. In neonates developing respiratory distress syndrome, however, the hypothyroxinaemia associated with prematurity is exaggerated. Consequently, screening programmes that initially measure thyroxine may require a further thyroxine estimation or supplementary thyroid stimulating hormone measurement, or both, to exclude hypothyroidism in such infants. In comparison, measuring thyroid stimulating hormone as the primary test circumvents consideration of either gestational maturity or respiratory distress syndrome, as thyroid stimulating hormone values are independent of these variables (present studies).[2 8] Further, routine measurement of thyroid stimulating hormone would facilitate the early identification and treatment of sick preterm neonates with permanent or transient hypothyroidism.[19 20] These points reinforce the argument favouring primary thyroid stimulating hormone measurement in the screening for congenital hypothyroidism.

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